1653

Attorney Docket No. 172.2US.DC2
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Bischofberger et al.

Serial No.: 09/801,164 Group No.: 1653

Filed: March 7, 2001 Examiner: D. Lukton

For: NUCLEOTIDE ANALOGS

Assistant Commissioner for Patents
Washington, D.C. 20231

AMENDMENT TRANSMITTAL

1. Transmitted herewith is an amendment for this application.

STATUS

2. Applicant is

☐ a small entity - verified statement:

☐ attached.

☐ already filed.

☒ other than a small entity.

CERTIFICATE OF MAILING (37 CFR 1.8 (a))

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Assistant Commissioner for Patents, Washington, D.C. 20231.

Robin Torres
(Type or print name of person mailing paper)

Date: July 26, 2002

(Signature of person mailing paper)

EXTENSION OF TERM

3. The proceedings herein are for a patent application and the provisions of 37 CFR 1.136 apply

(a) [x] Applicant petitions for an extension of time under 37 CFR 1.136 (fees: 37 CFR 1.17 (a)-(d)) for the total number of months checked below:

	Extension (months)	Fee for other than small entity	Fee for small entity
[x]	one month	$110.00	$55.00
[ ]	two months	$400.00	$200.00
[ ]	three months	$920.00	$460.00
[ ]	four months	$1,440.00	$720.00

Fee $ 110.00

If an additional extension of time is required please consider this a petition therefor.

[ ] An extension for _____ months has already been secured and the fee paid therefor of $ _____ is deducted from the total fee due for the total months of extension now requested.

Extension fee due with this request $ _____

OR

(b) [ ] Applicant believes that no extension of term is required. However, this conditional petition is being made to provide for the possibility that applicant has inadvertently overlooked the need for a petition for extension of time.

FEE FOR CLAIMS

4. The fee for claims (37 CFR 1.16(b)-(d)) has been calculated as shown below:

	(Col. 1)		(Col. 2)	(Col. 3)	SMALL ENTITY			OTHER THAN A SMALL ENTITY	
	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NO. PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE	ADDIT. FEE	*OR*	RATE	ADDIT. FEE
TOTAL *	1	MINUS **	20	= 0	X 9 =	$		X18=	$ 0
INDEP. *	1	MINUS **	3	= 0	X42=	$		X84=	$ 0
☐ FIRST PRESENTATION OF MULTIPLE DEP. CLAIM					+140=	$		+280=	$ 0
					TOTAL ADDIT. FEE	$	*OR*	TOTAL ADDIT. FEE	$ 0

(c) ☒ No additional fee for claims is required.

OR

(d) ☐ Total additional fee for claims required $ _____

FEE PAYMENT

5. ☐ Attached is a check in the sum of $ _____

☒ Charge Account No. 07-1250 the sum of $ 110.00

A duplicate of this request is attached.

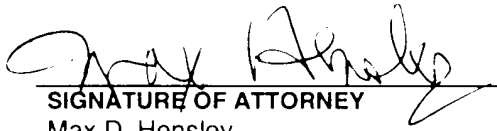
FEE DEFICIENCY

6. Authorization to Charge Additional Fees

☒ The Commissioner is hereby authorized by this document to charge any additional fees which may be required by this paper and during the entire pendency of this application to Account No. 07-1250 , except the issue fee at or before mailing of Notice of Allowance, pursuant to 37 CFR 1.311 (b).

Reg. No. 27,043

Tel. No.: (650) 522-5878



SIGNATURE OF ATTORNEY

Max D. Hensley

Type or print name of attorney

Gilead Sciences, Inc.

333 Lakeside Drive

P.O. Address

Foster City, CA 94404

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of	Group Art Unit: 1653
	Attorney Docket No. 172.2US.DC2
Bischofberger et al.	Examiner: D. Lukton
Serial No: 09/801,164	
Filed: March 7, 2001	
Title: NUCLEOTIDE ANALOGS	

AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

This is responsive to the Patent and Trademark Office action mailed March 28, 2002. A Request for One Month Extension of Time is submitted herewith, whereby the date for response is July 28, 2002.

Claim 52 is amended as shown in the attached mark-up. In addition, the specification basis for the R group, found at page 21, line 19 through page 23, line 2, has been amended to correspond to the amended claim 52, also as shown in the attached mark-up. Note that exemplary embodiments, for instance "including 2-, 3- and 4-methoxyphenyl and 2-, 3- and 4-ethoxyphenyl" were embedded in the original R group specification text but are not required for claim 52. However, these have been inserted

in the appropriate locations in the revised specification text in order to maintain the full original disclosure.

Claim 52 remains the sole claim in this application.

Claim 52 was rejected under 35 USC 112(2). Responding to the examiner's careful examination and helpful points:

1. The Markush format is now consistently used in the amended claims and disclosure.

2. The disclosure relating to the aryl R groups has been reorganized following the examiner's suggestions, plus applicants have clarified the aryl language. The examiner observes that no stable aryl groups are known having C_7-C_9. Applicants take the position that while this is true of the unadorned rings themselves, aryl as used in the present specification is intended to cover aryl which is either substituted or unsubstituted. Phenol, for example, would be an aryl group under this convention since it is phenyl substituted by OH. Applicants acknowledge the examiner's point, however. Thus, applicants have amended the specification and claim 52 in order to better present this substituent class, the basis for which is further discussed below.

Disclosure relating to substituted R group aryl is found in the original specification in at least two locations. One is at page 21, lines 24-25:

"2-, 3- and 4-alkoxyphenyl (C_1-C_{12} alkyl including 2-, 3- and 4-methoxyphenyl and 2-, 3- and 4-ethoxyphenyl)"

and another is at page 22, lines 2-6:

"alkoxy ethyl [C_1-C_6 alkyl including CH_2-CH_2-O-CH_3 (methoxyethyl) and phenoxymethyl], aryloxy ethyl [C_6-C_9 aryl (including phenoxy ethyl) or C_6-C_9 aryl substituted by OH, NH_2, halo, C_1-C_4 alkyl or C_1-C_4 alkyl substituted by OH or by 1 to 3 halo atoms]".

Combining these disclosures in a fashion apparent to the skilled artisan (and reciting the aryl ring to be phenyl as suggested by the examiner) yields the following language for the R group substituted aryl:

--phenoxymethyl, phenoxyethyl, and phenyl each substituted by C_1-C_{12} alkoxy, OH, NH_2, halo, C_1-C_4 alkyl, or by C_1-C_4 alkyl substituted by OH or by 1 to 3 halo atoms—

It should be noted that the extraneous carbon atoms beyond 6 in the term "C_6-C_9" are provided by the C_1-C_4 alkyl substituents, now encompassed in the foregoing language which thus makes it unnecessary to continue with the C_7-C_9 recitations.

3. Redundant recitations have been eliminated.
4. Two of the 3 alternative recitations for N-ethylmorpholinio have been eliminated in favor of the structural depiction.
5. "Adamantoyloxymethyl" is now recited as a single word as suggested by the examiner. The second (structural) adamantoyl compound is correctly named by the examiner and that term has been inserted in the claim and specification. The third adamantoyl compound adjacent to the structural depiction (like several other R groups – see below) duplicates the linking oxygen atom. When more accurately depicted it is merely a duplicate of adamantoyloxymethyl and therefore has been dropped.

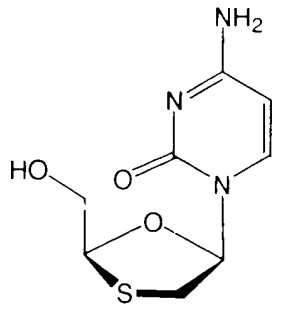
6. The space has been inserted.
7. The examiner is correct that the oxygen atoms have been accounted for twice and that "independent" is irrelevant. The draftsman was attempting to convey by divalency and the indication of the linking oxygen that these R groups are joined to form a cycle. This has been more explicitly set forth in the special language relating to joined R groups, which has been inserted after the long recitation of monovalent R groups.
8. The examiner's suggestion to subdivide the R substituents was a good one and applicants have adopted it.
9. The examiner is correct that the "N" and "O" substituents are in place of the chain carbon. Appropriate amendment has been made.

None of these amendments introduces new matter.

The examiner is requested to reconsider and withdraw the rejection under 35 USC 112(2).

Claim 52 was rejected under 35 USC 112(1) as not based on specification disclosure teaching any antiviral activity. The examiner is correct that no specification disclosure exists where these particular compounds were tested for antiviral activity. However, applicants believe that there is sufficient structural similarity to known antiviral compounds to substantiate the efficacy of the claimed genus.

Lamivudine is a known antiviral compound marketed for HIV and HBV therapy. It has the structure:



("Merck Index" 12th ed.)

Lamivudine is not the antivirally active moiety *in vivo*. In the body it is converted to the triphosphate at the 5′ hydroxyl group via an initial phosphorylation followed by diphosphorylation at the same site.

The presently claimed compounds are prodrugs of (or chemical intermediates for) the phosphonyl analogue of Lamivudine, i.e., the analogue in which the positions of the 5′ hydroxyl and methylene groups are inverted and linked to phosphorous via the inverted carbon atom. In order to provide the "pro" functionality, the hydroxyl substituents of the pentavalent phosphorus are esterified or amidated as described in the claims. Obviously, the esters or amides could be removed to produce the diacid of the phosphonate, i.e., they can be used a chemical intermediates to obtain the antivirally active Lamivudine analogue, or they are removed *in vivo* to generate the active compound.

A number of other related methoxyphosphonate nucleotide analogues are already known for their antiviral activity. These are more fully described in the specification, along with their antiviral uses, on pages 64-68.

Thus, adequate disclosure exists to support the asserted utilities. Moreover, while some compounds falling within the scope of the claim potentially may be inactive

antivirally, the specification contains adequate guidance for determining the active species. See specification pages 64 and 107-8.

The examiner is requested to reconsider and withdraw the rejection under 35 USC 112(1).

A clean copy of the amended claim 52 is attached, as is a clean copy of the corresponding specification pages as amended.

Applicants attach a new abstract, and following the examiner's instructions the substituent groups are not specified.

This application is now believed to be in condition for allowance. An early notice to that effect is solicited.

Respectfully submitted,

Max D. Hensley, Reg. No. 27,043
Vice President for Intellectual Property
Reg. 27,043
Phone: (650) 522-5878
Fax: (650) 522-5575
email: max_hensley@gilead.com

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